2025 ESMO SARCOMA AND RARE CANCERS
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LONG-TERM NIROGACESTAT TREATMENT IN ADULT PATIENTS WITH DESMOID TUMORS: UPDATED EFFICACY AND SAFETY FROM THE PHASE 3 DEFI TRIAL

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DECLARATION OF INTERESTS

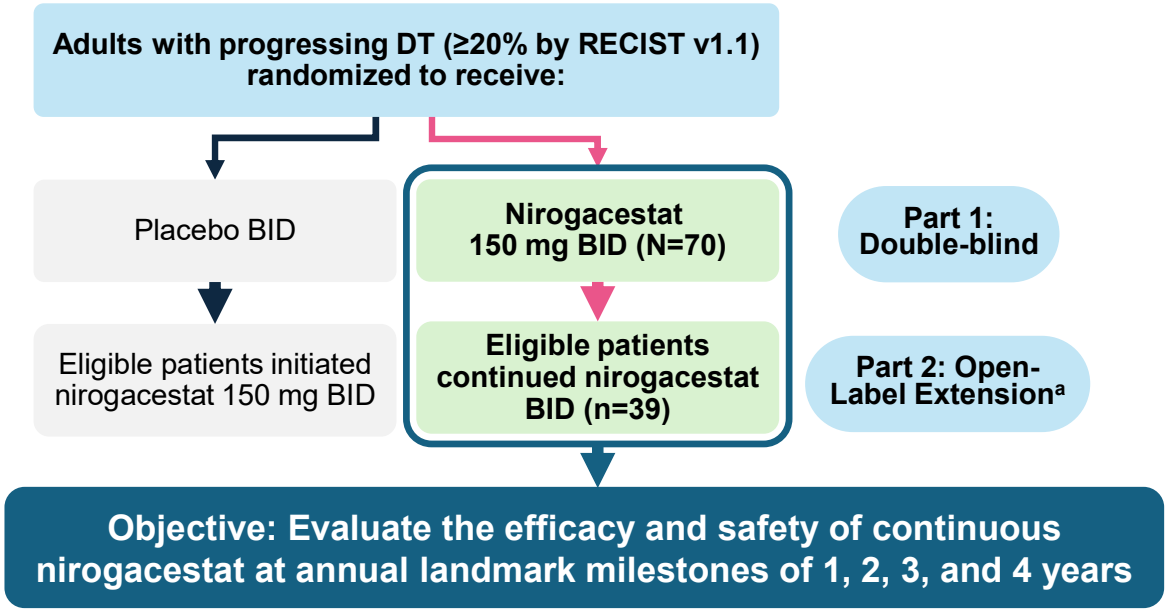
Dr. Bernd Kasper reports the following:

- Consulting/Advisory role for Ayala Pharmaceuticals, Bayer; Boehringer Ingelheim, GlaxoSmithKline, and SpringWorks Therapeutics, Inc.
- Honoraria from Bayer, GlaxoSmithKline, and Pharmamar-Zeltia; travel, accommodations, and expenses from SpringWorks Therapeutics, Inc.
- Research funding from Immunome, Cogent Medicine, PharmaMar, and SpringWorks Therapeutics, Inc.

The DeFi trial was sponsored by SpringWorks Therapeutics, Inc.

DEFI: A GLOBAL, RANDOMIZED, MULTICENTER, PLACEBO-CONTROLLED PHASE 3 TRIAL FOR NIROGACESTAT (NCT03785964)

DeFi Design



Nirogacestat: an oral, targeted gamma secretase inhibitor.[1] The only FDA-approved therapy for adults with progressing desmoid tumors (DT) who require systemic treatment.[2] Nirogacestat is currently under review by the EMA.[3]

DeFi Landmark Analysis

Population: Patients randomized to receive nirogacestat in the double-blind phase up to the final 19Dec2024 data cutoff

Endpoints:

- **Tumor Response and Durability** – Evaluated per RECIST v1.1
- **Patient Reported Outcomes** – BPI-SF; GODDESS DTSS TSS and DTIS PF; EORTC QLQ-C30 GHS/QoL, PF and RF
- **Safety** – Reported as TEAEs

[a]Following imaging-based progression or primary analysis completion, patients were unblinded and given the option to enroll in an open-label extension phase if eligible.

1. OGSIVEO® (nirogacestat) [package insert]. Stamford, CT: SpringWorks Therapeutics, Inc: 2023. 2. SpringWorks Therapeutics, Inc. SpringWorks Therapeutics Announces FDA Approval of OGSIVEO (nirogacestat) as the First and Only Treatment for Adults with Desmoid Tumors. Press Release. Nov 27, 2023. 3. SpringWorks Therapeutics, Inc. SpringWorks Therapeutics Announces European Medicines Agency Validation for Marketing Authorization Application of Nirogacestat for the Treatment of Adults with Desmoid Tumors. Press Release. Feb 29, 2024.

BID, twice daily; BPI-SF, Brief Pain Inventory-Short Form; DTIS PF, Desmoid Tumor Impact Scale Physical Functioning Domain Score; DTSS TSS, Desmoid Tumor Symptom Score Total Symptom Score; EMA, European Medical Agency; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire–Core 30; FDA, Food and Drug Administration; GHS/QOL, Global Health Status–Quality of Life Score; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; PF, Physical Functioning Score; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; RF, Role Functioning Score; TEAE, treatment-emergent adverse event.

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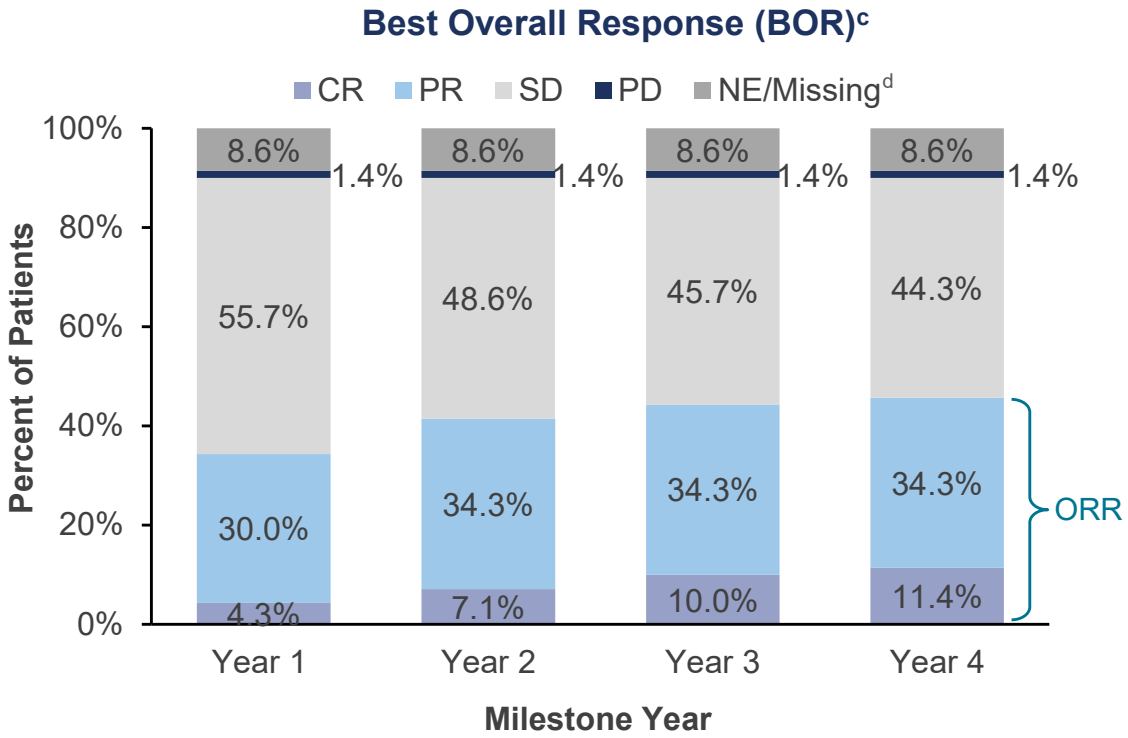
LANDMARK ANALYSIS OF BEST OVERALL OBJECTIVE RESPONSES

ORR in ITT Population, N=70[a]

- **Median (range) duration of nirogacestat exposure:** 33.6 (0.3–61.8) months
- **ORR[b] increased from 34.3% for patients staying on nirogacestat for up to 1 year to 45.7% for those on nirogacestat for up to 4 years**
  - 3 additional PRs and 3 additional CRs were reported across years 3 and 4
  - Total of 8 (11.4%) CRs were reported



Final data cutoff: 19Dec2024. [a]Enrolled patients who were randomized to receive nirogacestat in the double-blind phase. [b]ORR was defined as the proportion of patients having a BOR of CR or PR by RECIST v1.1. [c]BOR was defined as the best response obtained across all assessments per independent central review. PR and CR required confirmation by subsequent scans. [d]At each year, NE was 7.1% and Missing was 1.4%.
BOR, best overall response; CR, complete response; ITT, intent-to-treat; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PR, partial response; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; SD, stable disease.

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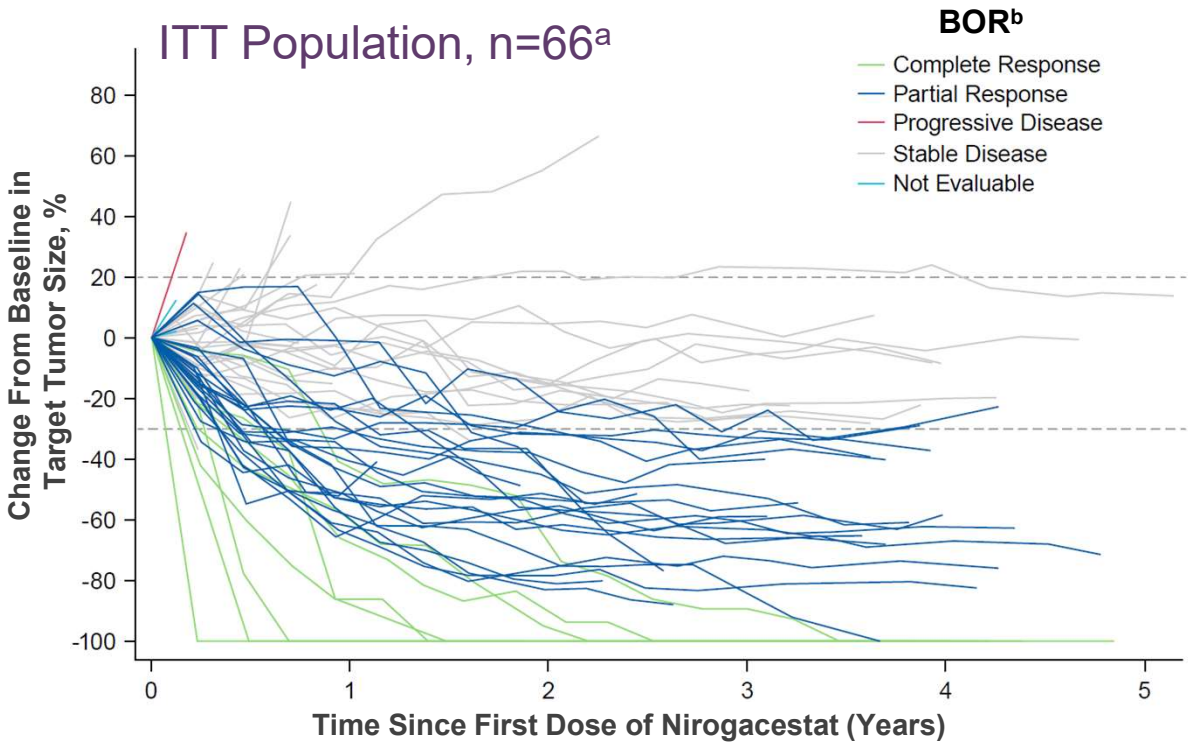
LONG-TERM NIROGACESTAT TREATMENT WAS ASSOCIATED WITH DURABLE TUMOR SIZE REDUCTIONS



- **Median best percent change** from baseline target tumor size per RECIST v1.1 improved at each annual milestone

Median % (min, max)

- at least 1 year of treatment (n=46): **−32.3 (−100, 6)**
- at least 2 years of treatment (n=40): **−42.5 (−100, 2)**
- at least 3 years of treatment (n=33): **−51.3 (−100, 2)**
- at least 4 years of treatment (n=15): **−75.8 (−100, 2)**

Final data cutoff: 19Dec2024. [a]1 patient had no tumor size assessments and 3 patients had missing postbaseline tumor size measurements. [b]BOR was defined as the best response obtained across all assessments per independent central review. Partial response and complete response required confirmation by subsequent scans.
BOR, best overall response; ITT, intent-to-treat; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

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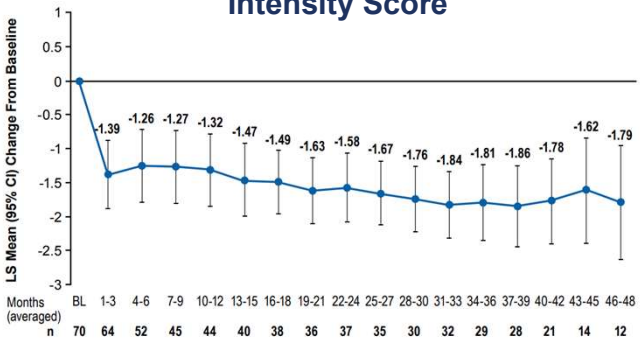
PATIENTS WHO REMAINED ON NIROGACESTAT TREATMENT SUSTAINED THEIR PRO GAINS FOR UP TO 4 YEARS

BPI-SF

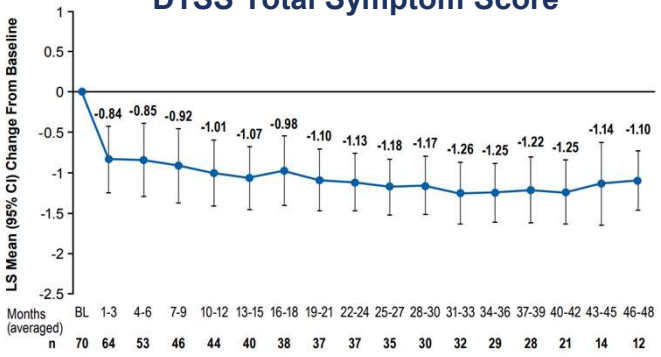
Average Worst Pain Intensity Score



LS mean change from baseline in BPI-SF average worst pain intensity score **ranged from −1.26 to −1.86** on a 0–10 scale

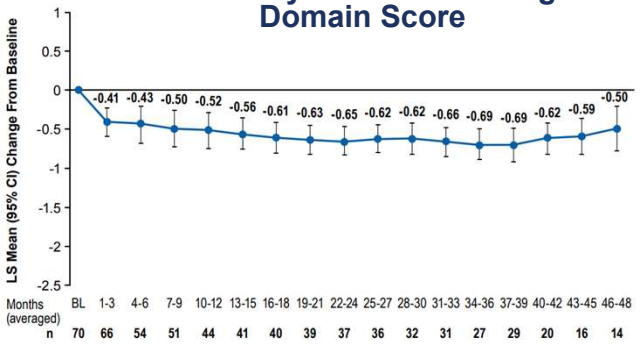
GODDESS

DTSS Total Symptom Score



LS mean change from baseline for DTSS total symptom score **ranged from −0.84 to −1.26** on a 0–10 scale

DTIS Physical Functioning Domain Score



LS mean change from baseline for DTIS physical functioning **ranged from −0.41 to −0.69** on a 5-point Likert scale

Final data cutoff: 19Dec2024. Based on the averaged results of 3-month intervals with DB and OLE data combined. For the patients with DB phase last dose and OLE phase first dose gap > 5 days, the gap was deducted for re-windowing. Mean (SD) baseline scores: BPI-SF 3.2 (3.23); DTSS-TSS 3.3 (2.33); DTIS-PF 2.8 (1.13). Average worst pain intensity score was up to a 7-day average of BPI-SF question #3: worst pain in last 24 hours (on a scale of 0–10). Total symptom score on a scale of 0–10 (24-hour recall, weekly summary scores based on 7-day average prior to each visit). Physical functioning domain score utilized a 5-point Likert for frequency (7-day recall).
BL, baseline; BPI-SF, Brief Pain Inventory-Short Form; DB, double blind; DTIS, Desmoid Tumor Impact Scale; DTSS, Desmoid Tumor Symptom Scale; GODDESS, GOunder/Desmoid Tumor Research Foundation DEsmoid Symptom/Impact Scale; LS, least squares; OLE, open-label extension; PROs, patient-reported outcomes.

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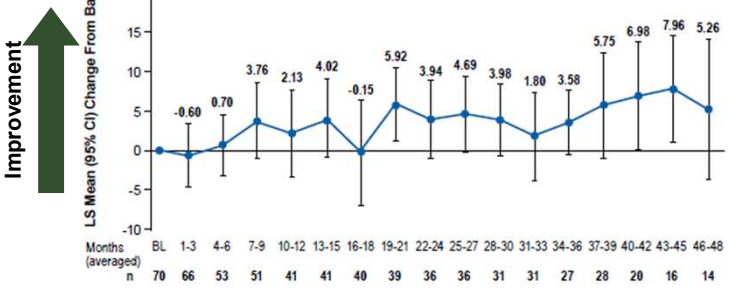
PATIENTS WHO REMAINED ON NIROGACESTAT TREATMENT SUSTAINED THEIR PRO GAINS FOR UP TO 4 YEARS

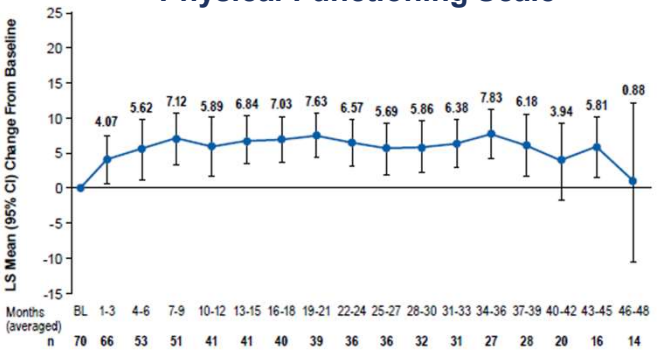
EORTC QLQ-C30

GHS/QoL Scale



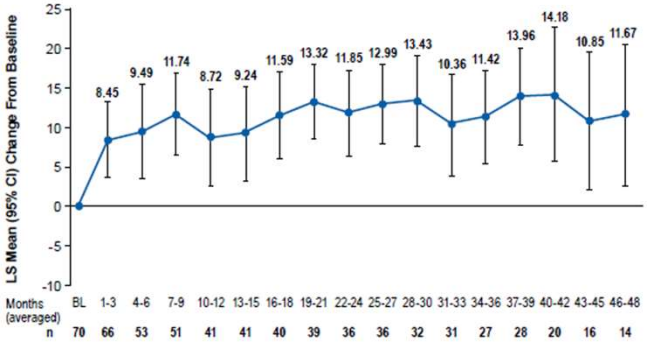
LS mean change from baseline in EORTC QLQ-C30 GHS/QoL score **ranged from −0.60 to 7.96** on a 0–100 scale

Physical Functioning Scale



LS mean change from baseline for EORTC QLQ-C30 physical functioning score **ranged from 0.88 to 7.83** on a 0–100 scale

Role Functioning Scale



LS mean change from baseline for EORTC QLQ-C30 role functioning score **ranged from 8.45 to 14.18** on a 0–100 scale

Final data cutoff: 19Dec2024. Based on the averaged results of 3-month intervals with DB and OLE data combined. For the patients with DB phase last dose and OLE phase first dose gap > 5 days, the gap was deducted for re-windowing. Mean (SD) baseline scores EORTC-QLQ-C30 GHS/QoL, 59.9 (24.38); EORTC-QLQ-C30-PF 77.5 (22.23); EORTC-QLQ-C30-RF 64.8 (32.67). Scale description: EORTC-QLQ-C30-GHS/QoL 1=very poor to 7=excellent, linearly transformed to a 0–100 scale. EORTC-QLQ-C30-PF and EORTC-QLQ-C30-RF: 1=not at all to 4=very much, linearly transformed to a 0–100 scale.
BL, baseline; CI, confidence interval; DB, double blind; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30; GHS, global health status; LS, least squares; OLE, open-label extension; PROs, patient-reported outcomes; QoL, quality of life.

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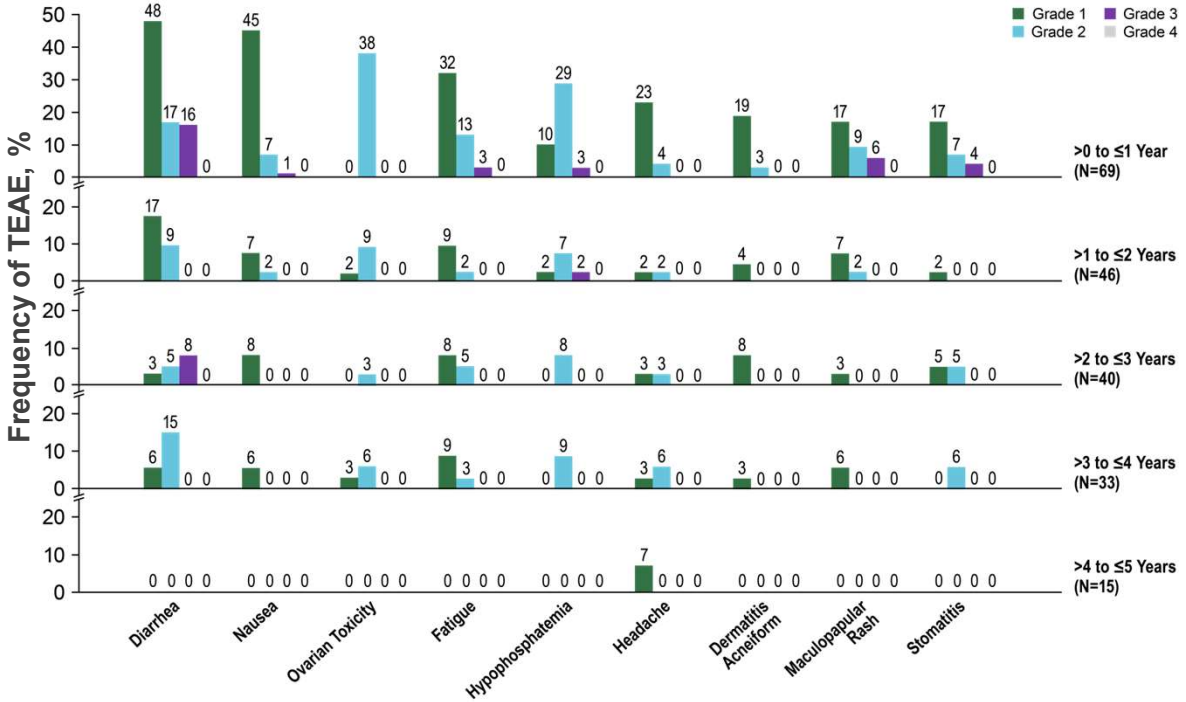
SAFETY PROFILE OF LONG-TERM NIROGACESTAT TREATMENT AND FOLLOW-UP ARE CONSISTENT WITH PRIMARY ANALYSIS

Safety Population, n=69[a]

- **Most frequently reported TEAEs:** diarrhea, nausea, ovarian toxicity (OT), fatigue, hypophosphatemia, and headache
  - Most TEAEs were Grade 1 or 2
  - Incidence and severity of frequently reported TEAEs decreased after year 1
- OT reports were consistent with the primary analysis[1,b]
  - 3 patients who had previously reported an OT event reported an additional event while continuing nirogacestat
  - 1 OT event in a patient who had not previously reported an OT event
- Since the primary analysis, dose reductions due to TEAEs occurred in 5 patients between years 2 and 3; no dose reductions occurred after year 3

New Onset of TEAEs Per Year by Greatest Severity[c]



Final data cutoff: 19Dec2024. [a]Patients who received at least one dose of nirogacestat. [b]Ovarian toxicity was identified by investigators (both verbatim term and grade) in females of reproductive potential based on abnormal reproductive hormone values or perimenopausal symptoms or both. The verbatim terms for ovarian toxicity events were coded to the MedDRA preferred terms of ovarian failure, premature menopause, amenorrhea, menopause, oligomenorrhea, and ovarian disorder. TEAEs were defined as events occurring or worsening after the initiation of nirogacestat through 30 days after the last dose or the date of the patient's last dose before starting another treatment. [c]New-onset TEAEs reported by ≥15% of participants are listed in order of frequency. MedDRA, Medical Dictionary for Regulatory Activities; TEAEs, treatment-emergent adverse events.

1. Ratan R, et al. Nirogacestat Treatment in Adult Patients with Desmoid Tumors: Long-Term Efficacy and Safety from the Phase 3 DeFi Trial. Oral presentation at the Connective Tissue Oncology Society Annual Meeting; Nov 13-16, 2024; San Diego, CA, USA.

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CONCLUSION

- These results show the long-term efficacy and safety of continuous use of nirogacestat with median exposure of 33.6 months, extended from 20.6 months at the primary analysis[1]
- Long-term treatment with nirogacestat was associated with:
  - improved objective response rate
  - further reduction in tumor size
  - sustained PRO gains (pain, DT-specific symptom severity and physical functioning, role functioning, and general health status/quality of life)
  - manageable safety profile
- Safety profile of long-term nirogacestat treatment was consistent with the primary analysis

1. Gounder MM, et al. *N Engl J Med*. 2023;388(10):898-912.
DT, desmoid tumor; PROs, patient-reported outcomes.

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Sarcoma Patient Advocacy Global Network (SPAGN)

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